

Effect of Radiation on the Human Reproductive System

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Irradiation may have a profound effect on reproductive function. The schedule of the delivered irradiation (total dose, number of fractions, and duration) is an important determinant of the radiobiological effect on the tissues involved and varies among different tissues and organs. Irradiation to the central nervous system may affect the timing of the onset of puberty, result in hyperprolactinemia, or cause gonadotropin deficiency if the hypothalamic-pituitary axis is involved in the radiation field. Direct irradiation to the testis will, in lower doses, affect the germinal epithelium: doses of irradiation greater than 0.35 Gy cause aspermia, which may be reversible. The time taken for recovery increases with larger doses; however, with doses in excess of 2 Gy aspermia may be permanent. At higher radiation doses (> 15 Gy), Leydig cell function will also be affected. In addition to radiation dose, the vulnerability of the testis is dependent on the age at irradiation and the pubertal status of the male. In the female, the response of the ovary to the effects of irradiation varies with age as well as dose, and separation of ovarian dysfunction into hormonal and fertility effects is not clearcut. An ovarian dose of 4 Gy may cause a 30% incidence of sterility in young women, but 100% sterility in women over 40 years of age. Pelvic irradiation may also have a profound effect on the uterus, with arrested growth in the prepubertal girl, and failure of uterine expansion during pregnancy with subsequent miscarriages and premature labor.

Introduction

Information about the impact of environmental radiation on reproductive function might be derived from studying the effects of radiation accidents in the community. There are, however, few reports of reproductive function following radiation accidents because the radiation doses are not accurately known, and the effects on fertility are rarely reported. The data may be extrapolated, however, from the known consequences of therapeutic irradiation and deliberate experimental exposure.

Cranial irradiation may damage the central nervous system, including the hypothalamic-pituitary axis leading to precocious puberty, hyperprolactinemia, and gonadotropin deficiency. Abdominal, pelvic, spinal, or testicular irradiation may directly affect the gonads, leading to infertility and impaired sex steroid production.

The biological response to radiation varies among different tissues and organs, and not only is the total dose of irradiation received important, but also the number of fractions and days over which it is delivered. For example, a single dose to the testis may be less damaging to the

germinal epithelium than the same dose received over several fractions, whereas the reverse is true for the ovary. The latency period before expression of gross tissue injury is in general dose dependent after low doses and dose independent after high doses because of the partial or total inhibition of cell renewal.

Effect of Irradiation on the Hypothalamic-Pituitary Axis

It is recognized that deficiency of one or more anterior pituitary hormones may follow therapeutic external irradiation when the hypothalamic-pituitary axis is within the radiotherapy field. The use of interstitial radiotherapy and heavy-particle therapy is also associated with endocrine deficits following the selective treatment of pituitary lesions.

The use of hypothalamic releasing hormones [thyrotropin-releasing hormone (TRH), growth-hormone releasing hormone (GRF), corticotropin-releasing hormone (CRF), and gonadotropin-releasing hormone (GnRH)] have shown that the pituitary deficiencies following radiotherapy for nasopharyngeal tumors are likely to be secondary to hypothalamic damage. This is further supported by the finding of galactorrhea and hyperprolactinemia in some of these patients (1).

Hyperprolactinemia has been widely reported following external radiotherapy to the hypothalamic-pituitary

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region (2-5): it is likely that it represents damage to the hypothalamus, resulting in deficiency of endogenous prolactin inhibitory factor. In a study of the changes in prolactin concentration in patients who had normal prolactin levels before radiotherapy (37.5-42.5 Gy over 20-22 days) for a pituitary tumor, there was a significant rise in mean serum prolactin with a peak at 2 years after radiotherapy followed by a gradual decline over the next 3 years (6). The hyperprolactinemia was noted to be more marked in female patients, a finding previously reported (1,7), although the reason is unclear. Further evidence that the hyperprolactinemia is due to hypothalamic damage is suggested by the rarity of this phenomenon after interstitial radiotherapy with yttrium-90 implants (8,9), in which the irradiation is almost exclusively confined to the pituitary gland. A possible explanation for the transient nature of the hyperprolactinemia, when all other radiation-induced anterior pituitary hormone deficiencies appear permanent, is that the radiation induced damage to the hypothalamic prolactin-inhibitory centers is followed by the evolution of direct damage to the pituitary lactotroph cells after an interval of several years. An alternative explanation for the low incidence of hyperprolactinemia after pituitary yttrium implants is that there may be hypothalamic damage, but the pituitary lactotroph may also have been directly damaged by the yttrium and unable to mount an appropriate prolactin response to deficiency of endogenous prolactin inhibitory factor.

The distinction between radiation-induced isolated hypothalamic damage and combined hypothalamic and pituitary damage is of more than academic interest. Homburg et al. (10) have described good results in women with organic pituitary disease treated with GnRH therapy to induce ovulation, providing that those who had undergone hypothalamic-pituitary irradiation were excluded, implying that in these latter patients direct radiation damage to the pituitary gonadotrophs impaired the gonadotropin response to pulsatile GnRH.

Gonadotropin Deficiency

Anterior pituitary hormone deficiencies after radiotherapy have been documented in five main groups of patients: those treated for nasopharyngeal carcinomas, those treated for tumors of the pituitary gland, those treated for primary brain tumors, children who have received prophylactic cranial irradiation for acute lymphoblastic leukemia, and patients who have undergone whole-body irradiation. The latter three groups are all assumed to have normal hypothalamic-pituitary function before radiotherapy, and retrospective studies therefore give an accurate estimate of the effects of irradiation. Patients with pituitary disease and nasopharyngeal carcinoma may, however, show pituitary hormone deficits as a consequence of the underlying tumor or surgical intervention before radiotherapy. It is therefore only the more recent prospective studies, which have examined pituitary function between presentation, surgery, and radiotherapy, which can adequately ascribe the subsequent pituitary dysfunction to the individual insults.

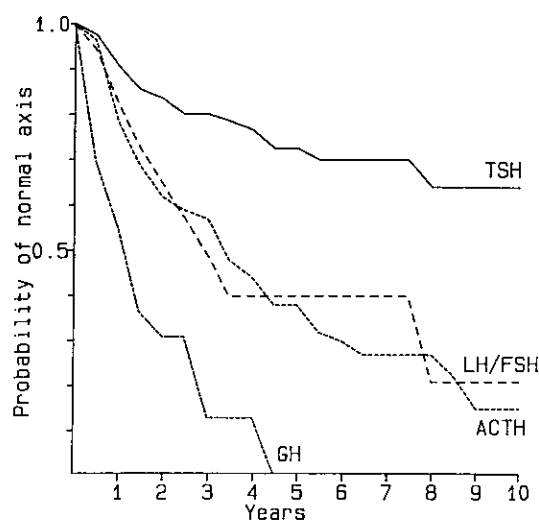


FIGURE 1. Life-table analysis indicating the probabilities of initially normal hypothalamic-pituitary axes remaining normal after radiotherapy.

Littlely et al. (6) have shown that following radiotherapy for pituitary tumors (20-45 Gy in 8-15 fractions over 10-22 days using linear accelerator equipment, 4 or 8 MeV), anterior pituitary hormone deficiency occurs in a well-defined order, with the growth hormone (GH) axis the most susceptible (Fig. 1). In two thirds of patients, gonadotropin deficiency occurs before adrenocorticotrophic hormone (ACTH) deficiency, but in the remaining third the order is reversed. Thyroid-stimulating hormone (TSH) secretion is the least vulnerable to such damage. By 3.5 years after this schedule of radiotherapy, 60% will be gonadotropin deficient, and by 8 years almost 80%. At any one time the prevalence of gonadotropin deficiency following irradiation will depend on the dose of irradiation, the radiation schedule, and the time elapsed since radiotherapy (Fig. 2). After low-dose cranial irradiation regimes such as used in leukemia prophylaxis, deficiency of anterior pituitary hormones other than growth hormone are uncommon (11).

In those patients who consistently receive the highest doses of irradiation to the hypothalamic-pituitary axis, such as those treated for nasopharyngeal carcinoma or rhabdomyosarcoma of facial structures, gonadotropin deficiency is common. In a series of 15 patients irradiated for nasopharyngeal tumors, (12), 12 had deficiencies of all anterior pituitary hormones. Endocrine investigations, including hypothalamic releasing factor tests, indicated that the hypothalamus was the primary site of radiation damage. The dose of irradiation ranged from 50 to 83 Gy, administered using cobalt 60, kilovoltage X-rays, and megavoltage X-rays. In a later study (13), 39 of 65 patients had hyperprolactinemia, providing further evidence of hypothalamic damage after external radiotherapy.

In their largest study to date, Samaan et al. (4) assessed 110 patients irradiated for nasopharyngeal carcinoma between the ages of 4 and 74 years and observed a progressive rise in the incidence of anterior pituitary hormone deficiencies with time. The endocrine investigations sug-

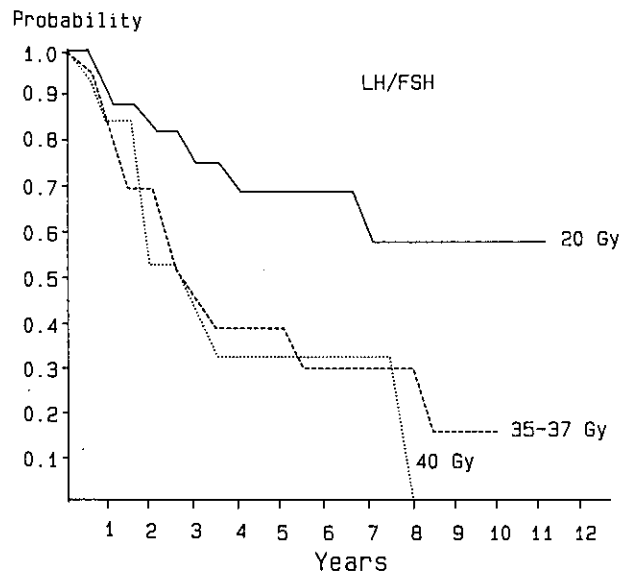


FIGURE 2. The probability of gonadotropin secretion remaining normal following radiotherapy, according to the dose schedules used: (—) 20 Gy in 8 fractions over 10–12 days; (---) 35–37.5 Gy in 15 fractions over 20–22 days; (.....) 40 Gy in 15 fractions over 20–22 days.

gested that both the hypothalamus and pituitary gland could be affected by the irradiation. In the children in this series (14 girls 13 years old or younger and 18 boys 14 years old or younger), there was a slightly higher incidence of both hypothalamic (81%) and pituitary (44%) dysfunction than in the group as a whole, lending support to the view that the immature hypothalamic-pituitary axis may be more vulnerable to radiation damage.

In a retrospective study, Huang (14) reported the assessment of hypothalamic-pituitary-gonadal function in 12 women 1–13 years after radiotherapy (60–65 Gy over 30–45 days) for nasopharyngeal carcinoma. Three were amenorrheic, three were oligomenorrheic, and eight had galactorrhea. Mean basal gonadotropin levels and the GnRH-stimulated gonadotropin levels were lower than normal controls. Five of the women with galactorrhea also had hyperprolactinemia, suggesting a hypothalamic lesion underlying the abnormalities of the reproductive axis.

In a prospective study of 31 patients irradiated for a nasopharyngeal tumor at a mean age of 43 years (7), the hypothalamus and pituitary received mean estimated doses of 40 and 62 Gy, respectively (24 fractions in 6 weeks). One year after treatment in the males, the mean basal and GnRH-stimulated follicle-stimulating hormone (FSH) concentrations were raised while the basal luteinizing hormone (LH) level was unchanged, but the GnRH-stimulated LH level was reduced. This dichotomy in FSH and LH patterns may be due to a radiation-induced alteration in pulse frequency of endogenous hypothalamic GnRH, affecting the relative secretion of LH and FSH from the pituitary (15). It is likely that in time frank gonadotropin deficiency will ensue, with low basal gonadotropin levels and reduced gonadotropin responses to GnRH.

Interstitial Therapy and Heavy Particles

In the treatment of pituitary tumors which are largely confined to the pituitary fossa, it has been the practice in some medical centers to administer large doses (up to 1500 Gy) of irradiation to the tumor by implanting seeds of radioactive yttrium-90 or gold-198. This therapy has also been used to ablate the pituitary gland in patients with metastatic malignancy and diabetic retinopathy. Yttrium-90 is a β -emitter, and therefore the radiation dose is well localized (16). There appears to be no damage to the hypothalamus, as demonstrated by the virtual absence of treatment-induced hyperprolactinemia in these patients (8,9). The consequences of ^{198}Au therapy are less well researched, but as a γ -emitter its effects may not be entirely confined to the pituitary region. Diabetes insipidus may occur following interstitial radiotherapy, presumably due to damage to the pituitary stalk or hypothalamus and has been reported as occurring transiently in as many as 50% of patients (17) and permanently in 1 of 16 patients treated for Cushing's disease (8). The early onset and recovery in the majority of cases suggests that this complication may be related to physical intervention rather than irradiation.

There may be deficiencies of all anterior pituitary hormones after interstitial radiotherapy with evidence of dose dependency. The relative sensitivity of the different axes appears to be GH first, followed by gonadotropins, ACTH, and TSH, the same order in which the axes are affected by hypothalamic damage due to external radiotherapy. Damage is almost entirely localized to the pituitary gland itself, with only two cases of radiation-induced hyperprolactinemia to suggest hypothalamic or pituitary-stalk damage (8). The relative radioresistance of the pituitary tissue is confirmed by normal residual function in the majority despite the very high doses of irradiation used (up to 1500 Gy). For example, one of 21 female patients developed GH deficiency, three showed partial ACTH deficiency, and none had evidence of treatment-induced TSH deficiency following ^{90}Y implantation for prolactinoma (18). More recently it has been suggested that the incidence of hypopituitarism may be extremely low after interstitial therapy with a relatively low dose of ^{90}Y (200–500 Gy) for prolactinoma (19), despite a high therapeutic efficacy.

Total Body Irradiation

Endocrine dysfunction has been reported after total body irradiation (TBI), which is usually used to prepare patients with hematological malignancies for bone marrow transplantation. Although impaired GH secretion after a single fraction dose of 10 Gy has been reported in children (20), the elevated basal and GnRH stimulated gonadotropin levels in patients with gonadal damage following their TBI and preparative chemotherapy suggests that gonadotropin secretion is intact. Similarly, in adults who received 12 Gy TBI in six fractions over 2 days, there was

no evidence of gonadotropin or any other pituitary hormone deficiency (21).

Precocious Puberty

Early and precocious puberty occurs in some children receiving cranial irradiation for brain tumors (22,23) and acute lymphoblastic leukemia (24). Although both sexes are affected, at lower radiation doses the female appears more vulnerable (24-26). The age of pubertal onset is positively correlated to the age at irradiation: the youngest at irradiation therefore have the most profound disturbances in the timing of puberty. By definition, gonadotropin deficiency is unusual in these children, which suggests that the CNS mechanism intrinsically responsible for restraining puberty is more vulnerable to the effects of radiation than gonadotropin secretion by the hypothalamic-pituitary axis.

Radiation and the Testis

The testis is one of the most radiosensitive tissues, with a direct radiation dose as low as 0.15 Gy causing a significant depression in the sperm count and temporary azoospermia occurring after doses of 0.3 Gy (27). Irradiation of the testis may occur during therapeutic and diagnostic procedures as well as from occupational exposure. The testis may receive a scattered dose from nearby pelvic or abdominal irradiation fields or be directly irradiated such as in the prophylactic or relapse treatment of leukemia. The allowable occupational radiation exposure level per year will probably have little effect on testicular function, but accidental exposure, for example, during nuclear reactor accidents, may result in whole body exposure at doses below the threshold for lethality but above those capable of inducing long-term sperm count depression.

An understanding of the process of spermatogenesis in normal men leads to a better appreciation of radiation effects on the testis. No proliferation occurs after irradiation of either Leydig or Sertoli cells. In general, lethally irradiated cells die during division. Differentiating spermatogonia are very radiosensitive, and after doses as low as 1 Gy both their numbers and that of their daughter cells, the preleptotene spermatocytes, are severely reduced (27). The doses of irradiation required to kill spermatocytes are higher than for spermatogonia (2-3 Gy results in an inability to complete maturation division, with a resultant decrease in spermatid numbers). Spermatids show no overt damage, but after 4-6 Gy the resultant spermatozoa are significantly decreased in number, signifying covert spermatid damage. Due to the radiosensitivity of spermatogonia, spermatocytes, and, ultimately, spermatids disappear from the testis after irradiation. The combined life span of spermatocytes and spermatids is about 46 days, and transport through the epididymis and vas deferens takes 4-12 days. Thus, during the first 50-60 days after low dose irradiation (1.5-2 Gy), sperm production remains above 50% of control values and then drops dramatically with resultant temporary oligo- or azoospermia. The time period for depletion of sperm is consistent

with the kinetics of spermatogenesis in the unirradiated testis, suggesting that the kinetics are not altered by irradiation. Higher doses cause a more rapid onset of oligospermia and azoospermia by a direct effect on the later stages as well as earlier stages of sperm production.

Recovery takes place from the surviving stem cells (type A spermatogonia), and proliferation of stem cells results in regeneration of stem cell numbers. Some spermatogonia differentiate, so that spermatocytes and later spermatids appear in the testis, resulting in repopulation of the germinal epithelium with germ cells. With single dose exposures, complete recovery (i.e., return to pre-irradiation sperm concentrations and germ cell numbers) takes place within 9-18 months after less than 1 Gy, 30 months for 2-3 Gy, and 5 or more years after 4-6 Gy.

The most precise and complete data on the effects of radiation on the testis are from studies on healthy volunteers from the Washington and Oregon state penitentiaries, who received 250 Kvp X-rays to the testes in a single dose (27-29). In these studies, pretreatment baseline hormonal and semen values were obtained for several months in each individual, radiation doses were accurately measured, and the volunteers were healthy, thereby eliminating both the complicating effects of disease and adjuvant chemotherapy on spermatogenesis. In each case the testicular tissue was fixed appropriately, permitting quantitative determination of cells at specific spermatogenic stages.

Irradiation of the testis during the radiotherapy treatment of cancer usually involves fractionated exposures. Under certain conditions, fractionation causes more stem cell killing than single dose treatments, although this has not been proven in man.

Hahn et al. (30) carried out serial semen analysis on 11 cancer patients who had received large pelvic field irradiation or interstitial ^{125}I seeds implanted in the prostate gland. Total calculated dose to the testis ranged from 1.18 to 2.28 Gy delivered in 24-35 fractions. All patients suffered temporary aspermia beginning about 3 months after irradiation. Recovery of spermatogenesis was first noted between 10 and 18 months after irradiation in five patients. The same group (31) studied a cohort of patients who received total fractionated doses of 0.19-1.78 Gy to the remaining testis following unilateral orchidectomy for seminoma. Azoospermia occurred in 10 of 14 patients who received over 0.65 Gy to the testis. Sperm reappeared in the semen within 30-80 weeks after the start of treatment.

Males in whom abdominal irradiation (inverted Y abdominal, pelvic, and inguinal fields) is given for Hodgkin's disease may receive a scatter dose of irradiation to the testes. Speiser et al. (32) studied 10 such men who received an average daily dose of 0.12 Gy, resulting in a total dose of 1.4-3.0 Gy. All were azoospermic, but only two patients were followed for longer than 16 months. Of the men studied retrospectively, 27.5% (33) were either oligospermic or had a normal sperm count following similar radiation treatment and scatter dosage to the testes, but the follow-up period was longer for these latter patients, suggesting that recovery of spermatogenesis may have taken place.

After fractionated courses of irradiation, azoospermia has been induced by a testicular dose as low as 0.35 Gy (34). After a radiation dose of between 2 and 3 Gy, the primary site of damage is the germinal epithelium, with recovery of spermatogenesis sometimes delayed for up to 10 years or more.

Tsatsoulis et al. (35) evaluated both Leydig and Sertoli cell function in 18 men 21–49 years old who had undergone unilateral orchidectomy for a testicular seminoma followed by 30 Gy irradiation in 20 fractions over 27–28 days to the remaining testis. Basal serum levels of testosterone, gonadotropins, and inhibin were estimated. The median testosterone level (12.7 nmole/L) was significantly less than in normal controls (20.0 nmole/L), and six men had levels below the normal adult male range. In addition, the median basal LH level was significantly higher (14.5 IU/L) than in controls (5.5 IU/L), and the testosterone/LH ratio significantly decreased suggesting Leydig cell damage. Damage to the germinal epithelium was confirmed by azoospermia, reduced inhibin levels compared with controls, raised FSH levels, and a lowered inhibin/FSH ratio.

In childhood, neither the threshold dose of irradiation required to damage the germinal epithelium, nor the dose above which irreversible damage occurs are known. The relationship between vulnerability to radiation-induced damage to the germinal epithelium and pubertal status is contentious, but the prepubertal testis may undoubtedly be damaged irreversibly by irradiation.

Low doses, 3–9 Gy, received as a scattered dose to the testes in 20 fractions over 4 weeks during the childhood treatment of a nephroblastoma resulted in oligo- or azoospermia many years later. Eight of 10 men studied between the ages of 17 and 36 years showed a greatly reduced sperm count (0–5.6 million), and 7 of these men had an elevated FSH level. All patients progressed through puberty spontaneously, and all except one, who had chronic renal failure, had normal LH and testosterone levels, indicating normal Leydig cell function (36).

With doses of direct testicular irradiation of 24–25 Gy, the germinal epithelium is completely ablated, and Leydig cell function is seriously affected in most patients. Ten of 12 boys showed evidence of Leydig cell dysfunction 10 months–8.5 years after testicular irradiation (24 Gy in 12 fractions over 18 days) for acute lymphoblastic leukemia, indicated by a low testosterone response to an acute bolus of human chorionic gonadotropin (hCG) or an increased basal plasma LH level, or both (37). Similar findings were reported by Leiper et al. (38). Shalet et al. (39) showed that Leydig cell failure occurs soon after irradiation, with no evidence of recovery up to 5 years after irradiation. Most of these boys therefore require androgen replacement therapy to enable normal pubertal development and to allow normal sexual function in adult life.

After the use of lower doses of testicular irradiation (12–15 Gy) for leukemia prophylaxis, Castillo et al. (40) reported normal pubertal development in 12 of 13 boys, with a normal basal testosterone level and testosterone response to hCG stimulation. Elevated basal or post-GnRH stimulated LH levels in the pubertal boys suggest subclinical Leydig cell damage is common. Seven boys

were old enough to perform semen analysis, and all were azoospermic.

Lower doses of testicular irradiation may be received by boys undergoing TBI for a bone marrow transplant or scatter from spinal fields used in craniospinal irradiation administered for some childhood brain tumors. The degree of testicular damage to the germinal epithelium and Leydig cell is dependent on the radiation dose and the age and pubertal stage of the boy (41).

Radiation and the Ovary

Information on the effects of irradiation on the ovary are derived from the studies of the previous use of pelvic radiotherapy for benign uterine bleeding and to restore normal menstruation in young women in the treatment of infertility. Further data have been acquired in women receiving irradiation to the ovary during the treatment of malignant tumors of the abdomen and during accidental exposure such as from the nuclear explosions of Hiroshima and Nagasaki.

The ovaries of a newborn girl contain a finite number of oocytes (about 2 million), which become reduced with increasing age. These oocytes are in the middle of a meiotic division that only becomes completed shortly before ovulation many years later, and mitotic multiplication of oocytes is therefore impossible. The population of oocytes continues to decline with age until menopause, when few oocytes survive.

After irradiation, damaged oocytes either undergo repair or are eliminated from the ovary by phagocytosis. The time at which degenerative changes occur is independent of the dose administered, but dose influences the number of oocytes affected.

The susceptibility to radiation-induced cell death depends on the developmental stage of the germ-cell at the time of exposure. The oogonia in prenatal life that are undergoing mitosis are highly susceptible to radiation-induced cell death. As the cells pass through the stages of meiotic division, resistance to radiation damage generally increases. Mammalian oocytes enter a prolonged resting phase shortly after birth, which persists throughout follicular growth and terminates shortly before ovulation. The radiosensitivity of the oocyte varies during the growth phase and is dependent on the age, the strain of the animal, and the species. In women, primordial oocytes are more resistant to the effects of radiation than oocytes in growing follicles.

The use of X-rays in the treatment of sterility between 1924 and 1957 (42) provided information on low dose irradiation of the ovaries. In three weekly sessions, a total estimated dose of 0.215 Gy was delivered to the pituitary and 0.065 Gy to the ovary. No deleterious effect was observed, and 308 of 794 women conceived and bore normal children.

Irradiation has been used for benign uterine bleeding for the return of normal menstruation. Of 1817 women treated with intrauterine radium for uterine bleeding (43), 311 were less than 40 years of age at irradiation, and 19 have subsequently become pregnant, with 33 conceptions.

There were 13 miscarriages, 7 stillbirths, and only 6 live births, 1 of whom was mentally retarded. The estimated radiation dose to the ovaries was 0.8 Gy in women less than 20 years and 1.2 Gy in ages 20–40 years. The radiation dose to the uterus was at least 24 Gy, an important factor in the high rate of miscarriage.

Although a permanent menopause can be caused in women at least 40 years old by a total radiation exposure of 4–7 Gy delivered in one to four fractions using 200–250 kV X-rays, estimates of the 50% probability level for permanent sterility in young women is approximately 20 Gy delivered over a 6-week period. If the radiation dose is delivered in a greater number of fractions, the damage to the ovary and consequent chance of infertility is likely to be less. In women with metropathia hemorrhagica treated with irradiation to induce an artificial menopause, Doll and Smith (44) found that 97% of 2068 women failed to menstruate again after two to four fractionated exposures to a total estimated ovarian dose of 3.6–7.2 Gy.

The treatment of Hodgkin's disease is influenced by the extent of the disease. Certain patients receive irradiation to the lymph nodes along the iliac vessels. As the ovaries lie in this area, they will receive a dose of about 35 Gy, which inevitably causes ovarian failure.

Transposition of the ovaries (oophoropexy) before irradiation with a consequent reduction in the dose to the shielded ovaries to a maximum of 6 Gy over 12–45 days has decreased the incidence of amenorrhea by over 50% (45). Nonetheless, the exact benefit derived from oophoropexy in women requiring inverted "Y" therapy is controversial. The extent of the disease needs to be carefully evaluated before considering oophoropexy, and then the procedure needs to be performed with accuracy and care.

Effect of Irradiation on Ovarian Function in Childhood

There have been few studies of ovarian function after irradiation uncomplicated by the effects of gonadotoxic, cytotoxic chemotherapy. Twenty-seven of 38 patients who received whole abdominal irradiation (20–30 Gy over 25–44 days) in childhood failed to undergo or complete pubertal development, and a further 10 later developed a premature menopause (median age 23.5 years). All had elevated FSH levels and low estradiol levels. Sex steroid replacement was required to induce breast development and prevent subsequent osteoporosis (46,47). Morphological studies after whole abdominal irradiation (20–30 Gy) have revealed marked inhibition of follicular growth and severe reduction in oocyte numbers (48). When flank irradiation rather than whole abdominal was used, only 1 of 15 girls developed pubertal failure. Only one patient, who developed pubertal failure after whole abdominal irradiation and required sex steroid therapy to acquire normal secondary sexual characteristics, showed evidence of reversibility of ovarian function with a documented conception at the age of 22.7 years (47). Recent studies have indicated that the spinal component of craniospinal irradiation for the treatment of brain tumors (49) and TBI before bone marrow transplan-

tation (50) may cause ovarian dysfunction due to radiation-induced ovarian damage.

It has been estimated from 18 girls who received 30 Gy, megavoltage, whole abdominal radiotherapy that the LD₅₀ for the human oocyte does not exceed 4 Gy (51), and in conjunction with the information about the position of the ovaries in relation to the radiation field, the predicted age at ovarian failure can be calculated approximately. This may provide a factual basis for fertility counseling in such patients who receive irradiation in childhood or young adult life.

Radiation and the Uterus

In those women in whom ovarian function is preserved but in whom the uterus has been involved in the radiation field, there is evidence that radiation changes to the uterus result in failure to carry a pregnancy, which has implications for *in vitro* fertilization in women with concomitant ovarian failure.

Following the treatment of benign uterine bleeding with intrauterine radium, in which the dose of irradiation received by the endometrium was at least 24 Gy, 13 of 33 conceptions ended in miscarriage, and a further seven were stillborn. In 38 women who received whole abdominal irradiation (20–30 Gy) during childhood (47), there were six conceptions in four patients, all ending in second trimester miscarriages. Critchley et al. (52) have studied these women in more detail by evaluating uterine physical characteristics and blood flow as well as assessing the functional uterine response to exogenous sex steroid replacement. Compared with women with premature ovarian failure not exposed to irradiation, those who received whole abdominal irradiation in childhood had a significantly smaller uterine length, implying that prepubertal exposure to irradiation may have an irreversible effect on uterine development and vasculature. In addition, in these latter women, the endometrium was unresponsive to physiological serum levels of estradiol and progesterone attained by exogenous administration. Doppler signals from the uterine arteries were absent in most. It is unclear whether this is a consequence of damage to the microvasculature of the uterus and associated blood supply or if the insult is at the level of the sex steroid receptors. As appropriate vascularization and subsequent growth of the endometrium are essential, however, for implantation and successful continuation of pregnancy, it is unlikely that women who have received abdominal irradiation in childhood will be able to sustain a pregnancy to term.

Conclusion

The gonads are highly sensitive to the effects of irradiation, with resultant temporary or permanent effects on fertility depending on the dose of irradiation received. In addition to the effect on the germ cells, sex steroid production may be impaired. In the adult this will result in symptoms of sex steroid deficiency and in the young child pubertal development will either not occur or be arrested. Irradiation to the head may have an effect on the timing of

the onset of puberty or on the hypothalamic-pituitary control of gonadotropin secretion, with subsequent infertility and sex steroid deficiency. These conclusions are derived from reports of known controlled radiation doses to individual patients. Nuclear atomic accidents will obviously have profound effects on the surrounding population. Global nuclear war resulting in less than lethal doses of emitted irradiation may render the surviving population sterile.

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